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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/719,993	11/24/2003	Michele Cargill	CL1496ORD	3651

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CELERA, AN APPLERA BUSINESS UNIT
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EXAMINER	
SWITZER, JULIET CAROLINE	
ART UNIT	**PAPER NUMBER**
1634	
MAIL DATE	**DELIVERY MODE**
12/10/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/719,993	CARGILL ET AL.	
	Examiner	Art Unit	
	Juliet C. Switzer	1634	

-- *The MAILING DATE of this communication appears on the cover sheet with the correspondence address* --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *5/25/07, 4/20/07, 4/6/07*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 36-70* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 36-70* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *24 November 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4/20/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. This office action is written in response to applicant's correspondence field 4/6/07 and 5/25/07. Claims 1 and 36-70 are pending.

Claim Rejections - 35 USC § 112- Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 1 and 36-70 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention and breadth of claims

Claims 1 and 36-70 are drawn to a method for identifying human who has an altered risk for developing Alzheimer's disease by detecting a SNP in SEQ ID NO: 7368 in said individual's

nucleic acids wherein the presence of the SNP is correlated with altered risk for Alzheimer's disease. Claim 44 specifically sets forth detecting a "C" at position 101 of SEQ ID NO: 7368 as indicative of an "increased" risk for Alzheimer's disease. Claim 53 specifically sets forth detecting a "T" at position 101 of SEQ ID NO: 7368 as indicative of an "decreased" risk for Alzheimer's disease. Claim 62 specifically recites that both the C is indicative of increased risk and the T is indicative of decreased risk. Thus the nature of the claimed invention requires the knowledge of a reliable association between alleles of a single nucleotide polymorphism present at position 101 of SEQ ID NO: 7368 and altered risk for developing Alzheimer's disease.

The invention is in a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The unpredictability of the art and the state of the prior art

Wang teaches the polymorphism elected for prosecution, namely, nucleotides 395-595 of SEQ ID NO: 5 taught by Wang (US 2003/0204075) are identical to instant SEQ ID NO: 7368, including the indication of a C/T polymorphism at position 495 of the sequence taught by Wang (this position aligns with instant position 101 of SEQ ID NO: 7368).

Further, the art teaches genetic variations and associations are often irreproducible. Hirschhorn et al. (Genetics in Medicine. Vol. 4, No. 2, pages 45-61, March 2002) teaches that most reported associations are not robust. Of the 166 associations studied three or more times, only 6 have been consistently replicated. Hirschhorn *et al.* suggest a number of reasons for the irreproducibility of studies, suggesting population stratification, linkage disequilibrium, gene-gene or gene-environment interactions, and weak genetic effects and lack of power are possible factors that lead to such irreproducibility. Hirschhorn *et al.* caution that the current irreproducibility of most association studies should raise a cautionary alarm when considering

their use as diagnostics and prognostics (p. 60, Col. 2). Thus, Hirschhorn cautions in drawing conclusions from a single report of an association between a genetic variant and disease susceptibility. Additionally, Ioannidis (Nature Genetics, Vol. 29, pages 306-309, November 2001) teaches that the results of the first study correlate only modestly with subsequent research on the same association (abstract). Ioannidis teaches that both bias and genuine population diversity might explain why early association studies tend to overestimate the disease protection or predisposition conferred by a genetic polymorphism (abstract).

Indeed, the unpredictability of the instantly claimed invention is specifically discussed in the post-filing date references of Bertram et al. (The American Journal of Human Genetics, Volume 79, pages 180-183) and Minster et al. (Neuroscience Letters 408(206) 170-172). In both of these references, the relationship set forth in the instant claims, namely between a polymorphism at position 101 of SEQ ID NO: 7368 and an altered likelihood of developing Alzheimer's disease were unable to be replicated. Further, it is noteworthy any association suggested by the data in Bertram et al. suggest that the opposite allele is related to disease (Bertram et al., p. 180). In response to the Bertram et al. paper, Grupe et al. (authorship including two of the instant inventors) state that "Further replication in well-characterized sample sets is required to assess whether the association is genuine (p. 184, Grupe et al. The American Journal of Human Genetics, Vol. 79, pages 183-184).

Thus, even given the data in the specification, due to the highly unpredictable nature of this technology area, it remains highly unpredictable whether or not a reliable association exists between the polymorphism at position 101 of SEQ ID NO: 7368 and risk for Alzheimer's disease.

Guidance in the Specification.

The specification provides no evidence that any polymorphisms within SEQ ID NO: 7368 is reliably associated with any risk for developing Alzheimer's disease.

The specification teaches a case-control genetic study to determine the association of a large set of SNP in the human genome with late onset Alzheimer's disease (Example beginning on page 117). The data suggest a putative relationship between the hCV8227677 SNP and late onset Alzheimer's disease in humans (see Table 6, page 5 of 6), however, in view of the high level of unpredictability in this technology area, these data are not sufficient to support the notion that there is a reliable association between alleles of this SNP and risk for Alzheimer's disease in humans.

The specification does not provide guidance for detecting a SEQ ID NO: 7368 SNP in "any" individual, only humans. Individual encompasses any human, dog, cat, mouse, ferret, gorilla, for example. The specification and the art do not provide any guidance that the polymorphic SNP is present in other animals or individuals. The specification appears to be directed to persons, i.e. humans. It is unpredictable other animals will have SEQ ID NO: 7368, the SNP and that the SNP is associated with Alzheimer's disease. Without further undue and unpredictable experimentation to determine whether the association is present over a range of individuals, a method for associating the SNP with a disease in any individual in unpredictable and undue.

The specification does not provide guidance for detecting any SNP within SEQ ID NO: 7368. The specification teaches a single SNP location in SEQ ID NO: 7368 at position 101. It is unpredictable that there are any other SNPs in SEQ ID NO: 7368 and the location of the SNPs if there are SNPs. Further the skilled artisan would be required to perform detailed analysis on each other position of SEQ ID NO: 7368 to determine if there is a polymorphism at the location and whether the polymorphism is associated with Alzheimer's disease. This experimentation is unpredictable and would require undue trial and error experimentation.

The specification and claims do not set forth teach what the increased risk is or decreased risk is relative to. The claim set forth increased risk or decreased risk when particular alleles are

present, but do not provide what the increase or decrease is in relation to. Increase and decrease in the abstract are relative terms.

Quantity of Experimentation

The quantity of experimentation in this area is extremely large since there is significant number of parameters which would have to be studied prior to being able to practice the claimed invention as broadly as written. This would require significant inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps.

Level of Skill in the Art

The level of skill in the art is deemed to be high.

Conclusion

In the instant case, as discussed above, in a highly unpredictable art where the art teaches the unpredictability of associating polymorphisms with disease, and in particular the hCV8227677 polymorphism with Alzheimer's disease, it is unpredictable any polymorphisms is associated with altered risk any Alzheimer's disease in any individual. Further, the prior art and the specification provides insufficient guidance to overcome the art recognized difficulties of association. Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the absence of a working example and the negative teachings in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

3. Claim 64 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a rejection for new matter. The examiner could not find any basis in the specification that teaches that SEQ ID NO: 7368 is within the LRP2 gene as represented by SEQ ID NO: 6756.

Response to Remarks

Applicant traverses the enablement rejection stating that the references cited by the Examiner to demonstrate the unpredictability of the technology area "support and bolster the results taught in the instant invention." Applicant points out that Hirschorn teaches real associations may not be reproducible if the underlying genetic effect is weak and if subsequent studies are small in size, and that failure to observe the **magnitude** of effects seen in the first study should not be taken as a repudiation of the association (emphasis added). In this case, based on the evidence of record, it is not possible to know if the results were not repeated simply because "the underlying genetic effect is weak," as Hirschorn suggested may happen in some cases. In this case the subsequent studies cited by the examiner did not fail to observe the same magnitude of effect, they failed to demonstrate any effect.

Applicant then analyzes the Bertram study pointing to potential reasons that might explain the discrepancies between the study presented in the instant specification and the Bertram study. First, it is noted that the analysis provided in the remarks of the Bertram study are attorney arguments that cannot replace evidence on the record. For example, applicant

suggests that there may have been inaccurate self reporting in the Bertram study that may have effected the results of the study. There is no evidence of such inaccuracy in the Bertram study on the record. Applicant further points out that the family based samples in Bertam included subjects with both early and late onset Alzheimer's disease, resulting in further reduction of power. Applicant's claims encompass analysis relative to both types of Alzheimer's disease.

Applicant's arguments do not address how the study provided by Minster et al. "support and bolster" the results taught in the instant specification. Minster et al. also failed to observe a significant effect between the hCV8227677 polymorphism and Alzheimer's disease. The study undertaken by Minster et al. is a case-control cohort study.

Given the totality of evidence on the record, the rejection is maintained and applied to the newly added claims.

1. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

4. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Juliet C Switzer whose telephone number is (571) 272-0753. The examiner can normally be reached on Monday, Tuesday, or Wednesday, from 9:00 AM until 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached by calling (571) 272-0735.

The fax phone numbers for the organization where this application or proceeding is assigned are (571) 273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571)272-0507.

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provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Juliet C. Switzer
Primary Examiner
Art Unit 1634

August 8, 2007